(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
15 November 2001 (15.11.2001)

PCT

(10) International Publication Number
WO 01/85725 A1

(51) International Patent Classification[7]: C07D 413/14, 413/04, 413/12, 263/58, 277/62, A61K 31/445, 31/4439, 31/428, A61P 25/16, 25/22, 25/24, 25/00, 25/30

(21) International Application Number: PCT/EP01/05320

(22) International Filing Date: 10 May 2001 (10.05.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
00201699.6 12 May 2000 (12.05.2000) EP

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(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

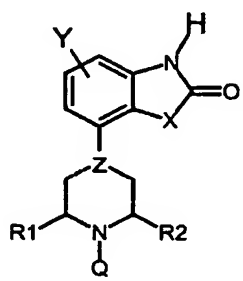
(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 01/85725 A1

(54) Title: PIPERAZINE AND PIPERIDINE COMPOUNDS



(I)

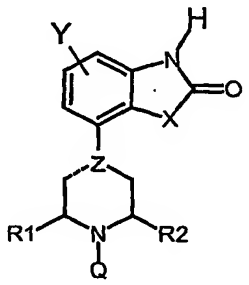
(57) Abstract: The invention relates to a group of novel piperazine and piperidine derivatives of the formula wherein Y is hydrogen, halogen, alkyl (1-3C), or CN, CF_3, OCF_3, SCF_3, alkoxy(1-3C), amino or mono- or dialkyl(1-3C) substituted amino or hydroxy, X is O, S, SO or SO_2, ---Z represents -C, = C or -N, R_1 and R_2 independently represent hydrogen or alkyl (1-3C), Q is benzyl or 2-, 3- or 4-pyridylmethyl, wich groups may be substited with one or more more substituents from the group halogen, nitro, cyano, amino, mono- or di (1-3C)alkylamino, (1-3C) alkoxy, CF_3, OCF_3, SCF_3, (1-4C)-alkyl, (1-3C)alkylsulfonyl or hydroxy,and salts and prodrugs thereof. It has been found that these compounds have interesting pharmacological properties due to a combination of (partial) agonism towards the members of the dopamine D_2-receptor subfamily and affinity for relevant serotonin and/or noradrenergic receptors.

New piperazine and piperidine compounds

The present invention relates to a new group of piperazine and piperidine derivatives having interesting pharmacological properties due to a combination of (partial) agonism towards the members of the dopamine D_2-receptor subfamily and affinity for relevant serotonin and/or noradrenergic receptors.

It is known from EP 0189612 that piperazine derivatives substituted at one nitrogen with a phenyl-heterocyclic group, and unsubstituted at the other nitrogen atom, have psychotropic activity.
Further it is known from EP 0190472 that benzofuran- and benzodioxole-piperazine derivatives substituted at the other nitrogen atom of the piperazine group, have also psychotropic activity.
Finally it is known from EP 0169148 that 1,3-dihydro-4-(1-ethyl-1,2,3,6-tetrahydropyridin-4-yl)-2H-indol-2-one and similar compounds have analgetic properties.

It has now surprisingly been found that a small group of piperazine and piperidine derivatives having formula (I)



(I)

wherein
- Y is hydrogen, halogen, alkyl (1-3C), or CN, CF_3, OCF_3, SCF_3, alkoxy(1-3C), amino or mono- or dialkyl(1-3C) substituted amino or hydroxy,
- X is O, S, SO or SO_2,
- ---Z represents -C, =C or -N,
- R_1 and R_2 independently represent hydrogen or alkyl (1-3C),
- Q is benzyl or 2-, 3- or 4-pyridylmethyl, wich groups may be substited with one or

more substituents from the group halogen, nitro, cyano, amino, mono- or di

(1-3C)alkylamino, (1-3C) alkoxy, CF_3, OCF_3, SCF_3, (1-4C)-alkyl, (1-3C)alkylsulfonyl or hydroxy, and salts and prodrugs thereof have a combination of (partial) dopamine D_2-receptor subfamily agonism and affinity for relevant serotonergic and/or noradrenergic receptors.

Preferred compounds according to the invention are compounds of the formula (I) wherein Y, R_1 and R_2 are hydrogen, X represents oxygen, and —Z and Q have the above meanings, and the salts thereof.

Especially preferred are the compounds wherein Y, R_1 and R_2 are hydrogen, X is oxygen, —Z represents -N and Q is optionally substituted benzyl.

Compounds according to the invention show affinities for at least two members of the dopamine D_2 receptor subfamily (pKi range 6.0 – 9.5) and a relevant serotonin (5-HT_{1A} , $5HT_{5A}$, $5HT_7$) receptor (pKi range 5.0 - 8.0) and/or noradrenergic (α_1, α_2) receptors, measured according to well-defined methods (e.g.: Creese I, Schneider R and Snyder SH, [^{3}H]-Spiroperidol labels dopamine receptors in rat pituitary and brain, *Eur J Pharmacol* 1997, **46**: 377-381 and Gozlan H, El Mestikawy S, Pichat L, Glowinsky J and Hamon M, 1983, Identification of presynaptic serotonin autoreceptors using a new ligand ^{3}H-PAT, *Nature* 1983, **305**: 140-142).

The compounds show varying activities as (partial) agonists towards members of the dopamine D_2 receptor subfamily and surprisingly towards the serotonin 5-HT_{1A} receptor and/or noradrenergic α_1 receptor. This activity in general was measured on the formation of adenylate cyclase in cell-lines expressing these cloned receptors (e.g. human D_2 receptors and 5-HT_{1A} receptors expressed in CHO cell line according to the methods described by Solomon Y, Landos C, Rodbell M, 1974, A highly selective adenylyl cyclase assay, *Anal Biochem* 1974, **58**: 541-548 and Weiss S, Sebben M and Bockaert JJ, 1985, Corticotropin-peptide regulation of intracellular cyclic AMP production in cortical neurons in primary culture, *J Neurochem* 1985, **45**:869-874).

The unique combination of (partial) dopamine D_2 -receptor subfamily agonism and affinity towards relevant serotonin- and/or noradrenergic- receptors results in a surprisingly broad activity in several animal models, predictive for psychiatric and/or neurologic disturbances.

The compounds show a surprisingly high efficacy in a therapeutic model for anxiolytic/antidepressant activity: the conditioned ultrasonic vocalization model in rats (see e.g.: Molewijk HE, Van der Poel AM, Mos J, Van der Heyden JAM and Olivier B (1995), Conditioned ultrasonic vocalizations in adult male rats as a paradigm for screening anti-panic drugs, *Psychopharmacology* 1995,**117**: 32-40). The activity of the compounds in this model was in the low microgram/kg range, which is surprisingly more active (by a factor 100 to 3000) compared to

the compounds previously described in EP 0190472 and EP 0398413.

In addition these compounds also show effects in models predictive for antidepressant activity at higher doses (forced swim test, see e.g.: Porsolt RD, Anton G, Blavet N and Jalfre M, 1978, Behavioural despair in rats: A new model sensitive to antidepressant treatments, *Eur J Pharmacol* 1978, **47**:379-391 and the differential reinforcement of low rates of responding model in rats, see e.g.: McGuire PS and Seiden LS, The effects of tricyclic antidepressants on performance under a differential-reinforcement-of-low-rate schedule in rats, *J Pharmacol Exp Ther* 1980, **214**: 635-641).

Depending on the degree of partial agonism towards the dopamine D_2-receptor subfamily, compounds tend to behave like full dopamine receptor agonists in induced climbing behaviour in mice, or, in the presence of a full dopamine receptor agonist, behave like a dopamine antagonist in the, *e.g.* apomorphine-induced climbing behaviour in mice (antagonism of apomorphine-induced climbing behaviour in mice, e.g.: Costall B, Naylor RJ and Nohria V, Differential actions of typical and atypical agents on two behavioural effects of apomorphine in the mouse, *Brit J Pharmacol* 1978, **63**: 381-382; suppression of locomotor activity, e.g.: File SE and Hyde JRG, A test of anxiety that distinguishes between the actions of benzodiazepines and those of other minor tranquillisers or stimulants, *Pharmacol Biochem Behav* 1979, **11**: 65-79). Compounds of the invention show potent efficacy in animal models predictive of anti-Parkinsonian activity. These include 6-OH-DA induced turning behavior in rats (Ungerstedt U, 6-OH-DA induced degeneration of central monoamine neurons, *Eur. J. Pharmacol.* 1968 5: 107-110), MPTP-lesioned Marmoset monkey (Nomoto M, Jenner P, Marsden CD: The dopamine agonist D_2 agonist LY 141865 but not the D_1 agonist SKF 38393, reverses Parkinsonism induced by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) in the common Marmoset. *Neurosci. Lett.*, (1985) 57: 37-41). Surprisingly, compounds of the invention lack the unwanted side effects associated with currently used dopaminergic drugs, including induction of stereotypy, nausea, dizziness and vomiting.
The compounds are of value in the treatment of affections or diseases of the central nervous system, caused by disturbances of the dopaminergic and/or serotonergic and/or noradrenergic systems, for example: addiction (including craving), anxiety disorders (including *e.g.* generalised anxiety, panic, obsessive compulsive disorder), depression, autism, schizophrenia, Parkinson's disease, disturbances of cognition and memory.

Suitable acids with which the compounds of the invention can form acceptable acid addition salts are for example hydrochloric acid, sulphuric acid, phosphoric acid, nitric acid, and organic acids such as citric acid, fumaric acid, maleic acid, tartaric acid, acetic acid, benzoic acid, p-toluene sulphonic acid, methane sulphonic acid and naphtalene sulphonic acid.

Prodrugs are derivatives of the compounds having formula (I) wherein a group is present which is easily removed after administration. Suitable prodrugs for example are compounds containing one of the following groups: amidine, enamine, a Mannich base, a hydroxy-methylene derivative, an O-(acyloxymethylene carbamate) derivative, carbamate or enaminone.

The compounds and the salts thereof can be brought into forms for administration by means of usual processes using auxiliary substances such as liquid and solid carrier materials.

The compounds of the invention can be prepared according to methods known for the synthesis of analogous compounds.

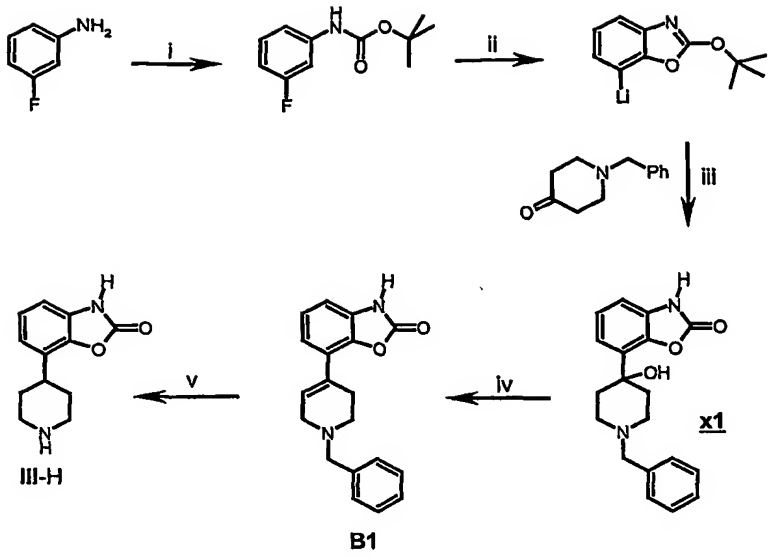
Method A

Compounds having formula (I) wherein ---Z represents –N or –C can be obtained by reacting the corresponding compound wherein Q is hydrogen with a compound Q-Hal, wherein Q has the above meanings and Hal is halogen, preferably bromine. This reaction can be carried out in a solvent such as acetonitrile in the presence of a base, for example ethyl-diisopropylamine or triethylamine.

The starting compounds wherein Q is hydrogen and ---Z is -N are known or can be obtained as described in EP 0189612. Starting compounds wherein Q is hydrogen and ---Z is -C can be obtained as described below in schema A.i (compound III-H).

Method B

The compounds B1, i.e compounds having formula (I) wherein ---Z represents =C can be obtained according to the method indicated in the following scheme A.i:



scheme A.I

The starting compound for step (ii) can be obtained according to the procedure described in J. Org. Chem. 45, (1980), 4789, and step (ii) itself can be carried out as described in J. Org. Chem., 47, (1982), 2804.

Step (iii) is carried out in a manner known for this type of chemical reactions.

The invention will be illustrated in the following Examples:

Example 1:

General Procedure for method A:

a) To 1 mmol of halide **Q**-Hal, 0.8 mmol of **I**-H (---Z = -N) dissolved in 7.5 ml of CH_3CN was added. Subsequently 0.43 ml (2.5 mmol) of $(i\text{-Pr})_2NEt$ was added and the resulting mixture was stirred for 3 hrs at 85 °C. After the reaction mixture had reached roomtemperature, 7.5 ml of dichloromethane were added, the resulting solution was put on top of a solid phase extraction column (Varian 5g type Si) and the fraction containing the desired product was subsequently put on top of a solid phase extraction column (Varian 5g 0.8 meq./g type Strong Cationic Exchange (SCX), conditioned on MeOH, then CH_2Cl_2)) after which the column was washed 2 times with MeOH. Then, the latter column, was washed with 0.1 M NH_3/MeOH and elution was performed with 1.0 M NH_3/MeOH. The eluate was concentrated *in vacuo* removing solvent and the rest of $(i\text{-Pr})_2NEt$, yielding the expected product.

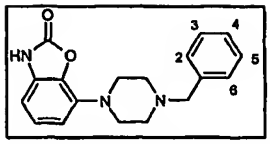
It is also possible to perform the purification with standard chromatographic procedures. In a single case (*i.e.* **A1**), the solvent used was dimethylformamide (DMF), see below.

b) 10.2 g (40 mmol) of I-H.HCl were suspended in 150 ml of DMF, to the stirred resulting mixture 21 ml (120 mmol) of $(i\text{-Pr})_2$NEt were added. During a period of 10 minutes a solution of 7.0 g (41 mmol) of benzylbromide in 25 ml of DMF was added at room temperature, the process is slightly exothermic (5-10 °C). Stirring was continued 3 hrs at room temperature after which the reaction mixture was poured on to 700 ml of water. Subsequently extraction was performed with 3x 250 ml of ethylacetate, the combined organic fractions washed with 2x 150 ml of water and dried with $MgSO_4$. Removal of the drying agent by filtration and of the solvent *in vacuo* yielded 10.5 g of raw product. The latter was purified by flash column chromatography (SiO_2, eluent CH_2Cl_2/MeOH 98/2), yielding 8.5 g (69%) of pure product **A1** as a free base, m.p.: 189-190 °C.

The compounds **A2** to **A46** as indicated in table A have been prepared analogously to procedure a) of method A.

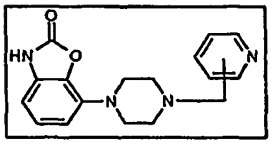
TABLE A

d = decomposition
fb = free base



				position(s) substitution(s)				
compound	Hal	salt	melting point °C	2	3	4	5	6
A1	Br	fb	189-90					
A2	Br	fb	220-22 d	Br				
A3	Br	fb	170-2 d	F	F	F	F	F
A4	Br	fb	220-2 d			CN		
A5	Br	fb	130-2 d		OMe			
A6	Br	fb	223-5 d			SO_2Me		
A7	Br	fb	235-7 d	Cl				Cl
A8	Br	fb	190-2 d	F	Me			
A9	Br	fb	200-2 d	F	F			
A10	Br	fb	122-4 d		SCF_3			
A11	Br	fb	>250 d	Cl			Cl	
A12	Br	fb	160-70 d	Me				
A13	Cl	fb	165-7 d			OMe		
A14	Br	fb	177-9		F	F		
A15	Br	fb	150-2			OCF_3		
A16	Br	fb	146-8		Br			
A17	Br	fb	193-5		Br	OMe		
A18	Br	fb	170-1		F	F	F	
A19	Br	fb	195-7	F		F		
A20	Br	fb	171-3	OCF_3				
A21	Br	fb	191-6 d		Cl	Cl		
A22	Br	fb	183-6		Me			
A23	Br	fb	132-4			CF_3		
A24	Br	fb	194-206 d		F		F	
A25	Br	fb	124-7		CF_3			
A26	Br	fb	184-6			tBut		
A27	Br	fb	216-8 d	Cl				
A28	Br	fb	115-20		CF_3	F		
A29	Br	fb	175-8	CF_3				
A30	Br	fb	186-8	Cl			CF_3	
A31	Br	fb	197-200	F		F		F
A32	Br	fb	159-63			Br		
A33	Cl	fb	152-8 d		Me	Me		
A34	Br	fb	178-83	F				
A35	Br	fb	215-9	CN				
A36	Br	fb	198-200		Me		Me	
A37	Br	fb	190-5			Me		
A38	Br	fb	166-76		CN			
A39	Br	fb	188-90	CF_3		F		
A40	Br	fb	210-4	Cl		F		
A41	Br	fb	180-6			F		
A42	Br	fb	159-63		F			
A43	Br	fb	178-80	F	Cl			

TABLE A (continued)



compound	Hal	salt	melting point °C	Q
A44	Cl	fb	188-90 d	2-pyridylmethyl
A45	Cl	fb	175-9	3-pyridylmethyl
A46	Cl	fb	230-5 d	4-pyridylmethyl

Example 2:

Step ii and iii (scheme A.i):

Under an inert atmosphere, 16.5 g (78.2 mmol) of N-(*tert*.butyloxycarbonyl)-*meta*-fluoroaniline were dissolved in 230 ml of dry tetrahydrofuran (THF) after which the solution was cooled to –75 °C (dry ice , acetone). While stirring, a solution of *tert*.butyl-lithium in heptane (ca. 156 mmol, 2 molequivalents) was added slowly after which the reaction mixture was stirred for 0.5 hrs at –70 °C, and subsequently for an additional 2 hrs at –25 °C. Again the reaction mixture was brought to –75 °C and a solution of 14.4 ml N-benzylpiperidone (78 mmol, 1 molequivalent) in 25 ml of dry THF. The reaction mixture was allowed to reach room temperature and stirred for an additional 16 hrs. Subsequently, 250 ml of 2M HCl was carefully added, the resulting mixture was extracted with EtOAc (3x). The water layer was, while stirring, poured on to 84 g of $NaHCO_3$ after which the waterlayer was again extracted with EtOAc. The resulting organic layer was dried on Na_2SO_4. After removal of the drying agent by filtration and of the solvent by evaporation *in vacuo*, 15 g of a dark yellow oil was isolated. Column chromatography (SiO_2, eluent: CH_2Cl_2/MeOH 9/1) yielded 7.5 g (ca. 30%) of a light yellow foam. While stirring, 1 g of the foam was triturated with di-ethyl ether and a small volume of EtOAc. After 50 hrs the solid material was filtered and washed with with di-ethyl ether/hexane to yield 0.5 g of a nearly white solid **x1**, mp 125-8 °C.

Step iv (scheme A.i):

While stirring, 6.3 g (19.4 mmol) of **x1** (scheme A.i.) was dissolved in 250 ml of dioxane after which 150 ml of concentrated HCl was added, the resulting mixture was refluxed for 1.5 hrs.
The reaction mixture was allowed to reach room temperature after which it was poured on to 140 g of $NaHCO_3$, subsequently about 250 ml of EtOAc were added and an amount of water enough to solve all of the solid material, the pH was >7. The layers were separated and the waterlayer was extracted with EtOAc (2x). The combined organic fractions (3), were dried on Na_2SO_4. After

removal of the drying agent by filtration and of the solvent by concentration *in vacuo*, 8 g of a dark yellow oil was isolated which solidified on standing. Column chromatography (SiO_2, eluent: EtOAc) yielded 4.56 g (ca. 30%) of a nearly white product. The latter was suspended in hexane and stirred for 20 hrs. Filtration and drying of the residue yielded 3.5 g (59%) of a white solid **B1** as a free base, mp ca. 153 °C.

Example 3:

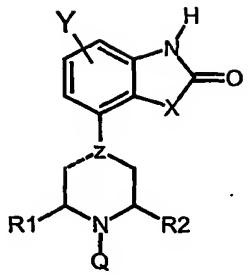
Preparation of intermediate III-H of scheme A.i.

Step v (scheme A.i):

2.71 g (8.9 mmol) of **B1** of scheme A.i. were dissolved in 250 ml of absolute EtOH. To the latter solution 0.6 g of 20% $Pd(OH)_2$ on carbon was added after which the reaction mixture was subjected to hydrogenation for 18 hrs at roomtemperature. Subsequently the reaction mixture was filtered (hyflo supercel) and the residu (hyflo) washed with methanol/triethylamine 97/3. The filtrate was concentrated *in vacuo* yielding 1.87 g of a nearly white solid which was suspended in EtOAc and stirred for 20 hrs. Filtration of the solid and subsequently drying afforded 1.56 g (81%) of the intermediate **III-H** (scheme A.i.).

Claims

1. Compounds having formula (I)



(I)

wherein

- Y is hydrogen, halogen, alkyl (1-3C), or CN, CF_3, OCF_3, SCF_3, alkoxy(1-3C), amino or mono- or dialkyl(1-3C) substituted amino or hydroxy,
- X is O or S, or SO or SO_2,
- ---Z represents -C, =C or -N,
- R_1 and R_2 independently represent hydrogen or alkyl (1-3C),
- Q is benzyl or 2-, 3- or 4-pyridylmethyl, wich groups may be substited with one or moresubstituents from the group halogen, nitro, cyano, amino, mono- or di (1-3C) alkylamino, (1-3C) alkoxy, CF_3, OCF_3, SCF_3, (1-4C)-alkyl, (1-3C)alkylsulfonyl or hydroxy,

and salts and prodrugs thereof.

2. Compounds as claimed in claim 1, wherein Y, R_1 and R_2 are hydrogen, X represents oxygen, Q is (substituted) benzyl and ---Z has the meaning given in claim 1.

3. Compounds as claimed in claim 2, wherein Q is benzyl and ---Z represents -N.

4. Method for the preparation of the compounds claimed in claim 1 by reacting a compound having formula (I) wherein Q is hydrogen, with a compound of the formula Q-Hal wherein Q has the meaning given in claim 1 and Hal is halogen.

5. Pharmaceutical compositions which contain at least one compound as claimed in claim 1 as an active component.

6. Method of preparing a pharmaceutical composition, characterized in that a compound as claimed in claim 1 is brought into a form suitable for administration.

7. A method of treating CNS disorders, characterized in that a compound as claimed in claim 1 is used.

8. A method of treating anxiety and/or depression, characterized in that a compound as claimed in claim 1 is used.

9. A method of treating Parkinson's Disease, characterized in that a compound as claimed in claim 1 is used.

10. A method of treating addiction, characterized in that a compound as claimed in claim 1 is used.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 01/05320

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D413/14 C07D413/04 C07D413/12 C07D263/58 C07D277/62
A61K31/445 A61K31/4439 A61K31/428 A61P25/16 A61P25/22
A61P25/24 A61P25/00 A61P25/30

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 97 36893 A (DUPHAR INT RES ;FEENSTRA ROELOF WILLEM (NL); KRUSE CORNELIS GERRIT) 9 October 1997 (1997-10-09)	1
X	page 1	7-10
A	EP 0 189 612 A (DUPHAR INT RES) 6 August 1986 (1986-08-06) cited in the application page 21; claim 1	1,5,7-10

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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PCT/EP 01/05320

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